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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,597	06/22/2000	David Duhl	1568.002/200130.472	8915

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	38

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,597	DUHL ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-16* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/18/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Information Disclosure Statement, filed 18 June 2002, has been entered into the record.

The Declaration of David Duhl, filed on 4 November 2002 under 37 CFR 1.132, has been entered into the record. The Declaration and submitted evidence are sufficient to overcome the claim rejections under 35 USC § 101 and 35 USC § 112, first paragraph, *in part* (see below).

The Amendment, submitted 17 September 2003 has been entered. Claim 10 was cancelled. Claims 11-16 were amended. Claims 1-9 and 17-25 were withdrawn by the examiner.

Claims 11-16 are under examination.

Informalities

Typographical

Claim 12 is objected to because one or more words appear to be missing. A descriptor word or phrase after "amino" appears to have been inadvertently removed. Amending the claim to replace "amino" with "an amino acid sequence," as recited in Claim 11, for example, would be remedial.

Appropriate correction is requested.

It is noted that Applicants have submitted Remarks pertaining to the patentability of the instant Invention under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, "Utility/Enablement." The Examiner agrees that there is overwhelming structural data and animal data that demonstrate that the polypeptide of SEQ ID NO: 2 is a plasmolipin that plays a role in neural development/remodeling. However, what is claimed in Claims 11 and 13-16, is a highly-variable derivative of SEQ ID NO: 2.

Claim Rejections/Objections

35 U.S.C. 101 and 35 U.S.C. 112, first paragraph- Utility/Enablement

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 13-16 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to a human plasmolipin-like protein, a polypeptide of 216 amino acids that resembles a proteolipid (p. 5, line 17, for example), and is found in the region of

chromosome 16 that may code for genes involved in Bardet-Biedl syndrome. Claims 11 and 13-16 encompass the polypeptide of SEQ ID NO: 2 "*except for at least one conservative amino acid substitution,*" and "epitope-bearing" portions of SEQ ID NO: 4. The specification does not disclose a function for the human plasmolipin-like protein of SEQ ID NO: 4 "*except for at least one conservative amino acid substitution*" and "epitope-bearing" portions of SEQ ID NO: 4" in the context of the cell or organism. Since the phrase "except for at least one conservative amino acid substitution" and "epitope-bearing" portions of SEQ ID NO: 4, encompass a very large number of peptides, the Specification is not enabling for the plasmolipin as claimed.

No well-established utility exists for newly isolated complex biological molecules. However, the specification implies the following as credible, specific and substantial patentable utilities for the claimed putative polypeptide:

1) For the treatment or prevention of a polypeptide mutation or deficiency involved or resulting in Bardet-Biedl syndrome.

2) For the diagnosis of Bardet-Biedl Syndrome or other diseases of the central or peripheral nervous system.

3) For chromosomal localization and/or tissue localization of polynucleotides encoding the claimed plasmolipin-like peptide.

4) For the production of antibodies.

5) To search for physiological activity of the claimed polypeptide or its ligands.

6) To detect ion-transport activity.

Each of these shall be addressed in turn:

1) *For the treatment or prevention of a polypeptide deficiency involved or resulting in Bardet-Biedl syndrome.* This implied utility is specific, however it is neither credible nor substantial. The specification does not disclose a link between Bardet-Biedl Syndrome and a deficiency in the polypeptide as claimed. Significant further experimentation would be required of the skilled artisan to identify individuals who would benefit from this sort of procedure, and then to determine a best course of treatment. Therefore, the implied utility is not credible. Additionally, there is no disclosure of whether the polypeptides could be administered, for example, orally or parenterally, nor the dosages needed, nor how to assay for improvement or intolerable levels of side effects, etc. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) *For the diagnosis of Bardet-Biedl Syndrome or other diseases of the central or peripheral nervous system.* Similarly, this asserted utility is credible and specific; however, it is not substantial. The specification does not disclose a link between the claimed polypeptide(s) and BBS, nor does it disclose *any* diseases associated with altered levels or forms of the plasmolipin-like polypeptide as claimed. Significant further experimentation would be required of the skilled artisan to identify individuals having deficits in the claimed polypeptide, and then correlating that deficit with a clinical syndrome. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) *For chromosomal localization and/or tissue localization of polynucleotides encoding the claimed plasmolipin-like peptide.* This asserted utility may be credible, but it is neither substantial nor specific. Applicant refers, for example, to the use of an RNA hybridization

probe for detection of nerve injury, and implies chromosomal localization to detect genes involved in BBS. However, probes and primers can be designed from any polynucleotide sequence; thus the asserted utility is not specific. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) *For the production of antibodies.* This asserted utility is credible and substantial, but not specific. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility.

5) *To search for physiological activity of the claimed polypeptide or its ligands.* Similarly, this asserted utility is credible and substantial. However, it is not specific. Such is performed for any peptide-ligand pair when the physiological role of each is not known. It is the definition of the type of further research that is required for either the claimed polypeptide or the ligand to have patentable utility.

6) *To detect ion-transport activity.* This asserted utility is credible and substantial. However, it is not specific. Such assays can be performed with any channel-forming polypeptide. Hence, the asserted utility is non-specific. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Claims 11 and 13-16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or

a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 11 and 13-16 are directed to a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 "except for at least one conservative amino acid substitution." The claims also recite epitope-bearing portions of SEQ ID NO: 4.

The specification teaches the plasmolipin-like polypeptide of SEQ ID NO: 4. However, the specification does not teach functional or structural characteristics of the plasmolipin-like polypeptide.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene

superfamilies in nature, then most homologues must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make biologically active plasmolipin-like protein without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

The specification does not teach the skilled artisan how to use the claimed plasmolipin-like protein(s) for any purpose. For example, a disclosure that definitively correlates a particular disease state, such as Bardet-Biedl Syndrome, to an alteration in levels or forms of the plasmolipin-like protein, in addition to SEQ ID NO: 4, might enable use of the claimed polypeptide as a diagnostic tool. However, the skilled artisan is not provided with sufficient guidance to use the polypeptides as claimed for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the claimed polypeptide such that it can be determined how to use the claimed plasmolipin-like protein and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex

nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

35 U.S.C. 112, first paragraph- Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are directed to a human plasmolipin protein, a polypeptide of 216 amino acids that resembles a proteolipid (Specification, page 5, line 17, for example), and is found in the region of chromosome 16 that codes for genes involved in Bardet-Biedl syndrome. Recent research papers indicate that plasmolipin is an ion channel expressed in Schwann cells and oligodendrocytes (Hamacher, et al, 2001, Mammalian Genome 12: 933-937), and is probably involved in apoptotic "pruning" during neural development and remodeling (Gleichmann, et al, 1996, Euro. J. Neurosci., 8: 405-414; Brancolini, et al, 1999, Mol. Biol. Cell, 10: 2441-2459).

Significant research evidence indicates that a mutation or deletion of the human plasmolipin gene contributes to the neuropathies characteristic of Bardet-Biedl syndrome.

The specification teaches a plasmolipin polypeptide (SEQ ID NO: 4). However, the specification does not teach functional or structural characteristics of all polypeptides and polypeptide fragments encompassed by the claims. The claims are directed to polypeptides with "at least one conservative amino acid substitution," as well as small antigenic fragments of SEQ ID NO: 4. However, the description of one plasmolipin-like polypeptide species (SEQ ID NO: 4) or one plasmolipin-like polypeptide from residues 2-218 of SEQ ID NO: 4, is not adequate written description of an entire genus of functionally equivalent polypeptides.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The plasmolipin polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4, or residues 2-218 of SEQ ID NO: 4- but not the full breadth of the claims- meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

Claims 11 and 13-16 are rejected for the reasons cited above.

Claim 12 is objected to.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW

4/11/04

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER